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Neurological Effects of Exposure to Non-Hypoxic Hypobaria

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14. ABSTRACT

The objective of this study was to investigate the neurological effects of exposure to non-hypoxic hypobaria following an outbreak of neurological decompression sickness in U-2 pilots. Eighty-three altitude chamber personnel (PHY), 105 U-2 pilots (U2P), and 162 age and medically matched doctorate degree controls (DOC) underwent high-resolution magnetic resonance imaging. Eighty-seven U-2 pilots underwent neurocognitive testing and were compared to 83 USAF pilot controls (AFP). White matter hyperintensities (WMH) are more prevalent in PHY (volume $p=0.020$/count $p=0.040$) and U2P (volume $p<0.001$/count $p<0.001$) when compared to DOC, while PHY is not significantly different than U2P. Lower neurocognitive performance in the domains of reasoning/calculation ($p=0.001$), memory ($p=0.036$), information processing accuracy ($p=0.032$), and general cognitive functioning ($p=0.004$) was demonstrated in U2P compared to AFP. Lower neurocognitive test performance within the U2P shows lower performance in the domains of reasoning/calculation, memory, general cognitive functioning, and general cognitive proficiency in U2P with higher WMH burden compared to U2P with lower WMH burden. This study provides strong evidence that non-hypoxic hypobaric exposure in U2P and PHY is associated with subcortical WMH in a young, healthy population lacking other risk factors for WMH and adds this occupational exposure to other environmentally related potential causes of WMH. This study also demonstrates measurable lower neurocognitive test performance in otherwise highly functioning U2P compared to AFP and furthermore demonstrates higher WMH burden is associated with lower neurocognitive test performance.

15. SUBJECT TERMS
Neurological decompression sickness, non-hypoxic hypobaria, high-altitude pilots, U-2, white matter hyperintensities

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1.0 EXECUTIVE SUMMARY

The purpose of this study was to characterize the neurological injury occurring in aircrew and chamber personnel in association with exposure to non-hypoxic hypobaria, relate the injuries to commonly accepted risk factors, and identify chronic neurological or neuropsychological impact. High-resolution magnetic resonance imaging was performed on 106 U-2 pilots, 83 altitude chamber personnel, 162 doctorate degree age- and health-matched controls, and 50 flight surgeons. Computerized neurocognitive testing was performed on 105 U-2 pilots. The hypobaric exposure experience (pre-exposure denitrogenation with 100% O_2, exposure to altitude) is associated with increased white matter hyperintensity (WMH) burden on fluid attenuated inversion recovery magnetic resonance imaging. Performance on computerized neurocognitive tests demonstrates an apparent acquired difference between U-2 pilots and U.S. Air Force pilot controls with the suggestion that this difference segregates in association with the WMH burden. Ongoing research will further analyze these data, attempt to develop an animal model, further investigate the underlying pathophysiological basis of these WMH changes, and pursue investigation into the long-term consequences of these changes.

2.0 BACKGROUND AND OBJECTIVE

Neurologic decompression sickness (NDCS) is a common but underreported condition that affects high-altitude pilots [1]. Neurologic symptoms associated with NDCS include syncope, nausea, disturbances of equilibrium and coordination, large sensory and motor tract dysfunction, amnesia, aphasia, hallucinations, tremor, and headaches [2]. Variable degrees of neurological recovery may occur. The number of severe NDCS episodes in high-altitude U-2 pilots increased in the period 2002-2009, including five near-fatalities, potentially related to an increased operations tempo [3]. The risk of DCS per flight increased from 0.076% pre-2006 to 0.23% during the 2006-2010 operation years with 44% diagnosed as NDCS [3]. Notably, no acute clinical symptoms or findings consistent with spinal cord involvement/injury were noted. This dichotomy in clinical signs compared to SCUBA diver NDCS suggests these pilots may have experienced cerebral neurological injury as a consequence of the NDCS episode. Although risk for clinical NDCS is relatively small, potentially the entire exposed population would be at risk for subclinical brain injury, raising concern about the long-term impact in aircrew.

Altitude chamber personnel are a second population subjected to non-hypoxic hypobaric exposure that occurs when chamber personnel provide essential safety monitoring during aircrew hypobaric hypoxic awareness training. If the neurological injures occurring in high-altitude pilots are related to exposure to non-hypoxic hypobaria, this second population would potentially have similar risks and findings.

Chronic brain injury in other neurological diseases is associated with lower neurocognitive performance. Specifically, subcortical white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) are important markers of cerebral integrity in both aging and brain disorders [4], are linked to executive functioning, processing speed, and general neurocognitive status [5-7], and are important predictors of increased neurocognitive decline [8-11]. If personnel exposed to non-hypoxic hypobaria suffer permanent brain injury, lower neurocognitive performance on standardized tests may occur even in the absence of clinical symptoms.

The objectives of this study were as follows:

(1) Identify the prevalence of abnormalities on MRI in the U-2 pilot population.
(2) Correlate the degree of abnormalities with the clinical presence of NDCS.
(3) Identify the prevalence of abnormalities on MRI in altitude chamber personnel.
(4) Identify neurocognitive test performance differences in U-2 pilots compared to U.S. Air Force (USAF) pilot controls.
(5) Correlate the neurocognitive test performance differences with MRI changes.
(6) Examine common risk factors for NDCS and compare these to MRI changes.

3.0 METHODS

3.1 Participants

The study was reviewed and approved by the Air Force Research Laboratory Institutional Review Board (AFRL/IRB). All participants were active duty members of the U.S. military recruited with strict adherence to Department of Defense requirements regarding protection of human subjects in research. Participation in this study was voluntary, and commanding officers were not involved in, or knowledgeable of, participation. All participants acknowledged this was not an anonymous study and provided informed consent prior to testing. All participants were between the ages of 26 and 50. All participants were healthy without any history of neurological or psychiatric disease and all had undergone annual medical examinations within 12 months of participation. All participants at the time of testing met USAF Flying Class II neurological standards, all pilots and flight surgeons were currently on active flying status, and all chamber personnel were currently certified to perform chamber duties.

(1) U-2 pilots (U2P): All active duty USAF U-2 pilots were invited to participate; 106 individuals agreed, exceeding a 90% participation rate. Sixteen (15%) reported symptoms of NDCS, with only two reporting more than a single episode.
(2) Altitude chamber personnel (PHY): All active duty altitude chamber personnel were invited to participate; the first 83 subjects who responded and met study entry criteria were accepted. All chamber personnel had experienced more than 50 occupational exposures over 20,000 feet altitude. Two (2.4%) noted the occurrence of NDCS symptoms.
(3) Doctorate degree control (DOC): All active duty military members with a doctorate degree assigned to duty within the continental United States were eligible to participate as normal controls, although recruitment was predominantly from the two San Antonio graduate medical education military facilities through presentations at professional staff meetings. Although the initial goal was 212, funding and availability issues restricted enrollment to the first 204 that responded. Subsequently, 31 were disqualified for failure to meet medical flight standards. Additionally, eight were unavailable secondary to duty requirements. This left 165 available for study. Of these, quantitative MRI imaging data are available on 162.
(4) Flight surgeon (FSG): All active duty military flight surgeons assigned to duty within the continental United States were invited to participate through announcements disseminated through the major commands and presentations at aerospace medical meetings. Although the initial goal was 82, funding issues and availability limited enrollment to the first 50 that responded. As a consequence of underenrollment and

failure to meet the minimum number established by the statisticians as necessary for meaningful interpretation, no further analysis was performed on this group.

(5) USAF pilot control (AFP): Data on 83 age-matched pilots were abstracted from the USAF School of Aerospace Medicine (USAFSAM) neurocognitive database.

(6) MRI calibration (CAL): Thirteen U2P were dual imaged on the Research Imaging Institute (RII), San Antonio, TX, and 59th Medical Wing (59MDW), Lackland AFB, TX, MRI scanners.

3.2 Facilities

(1) Structural MRI data on U2P were collected at RII, University of Texas Health Science Center, San Antonio, TX, using a Siemens 3T Tim Trio scanner equipped with a 12-channel phase array coil.

(2) Structural MRI data on PHY, DOC, and FSG were collected at Wilford Hall Ambulatory Surgery Clinic (WHASC), 59MDW, Lackland AFB, TX, using a Siemens 3T Verio scanner equipped with a 32-channel phase array coil.

(3) Neurocognitive testing was performed at the 9th Medical Group, Beale AFB, CA, and USAFSAM Neuropsychiatry Branch (FECN) at 59MDW, Lackland AFB, TX.

(4) Office space for USAFSAM/FECN research study personnel was provided by 59MDW, Lackland AFB, TX.

3.3 Experimental Design

Quantitative high-resolution 3T MRI on U2P and PHY was compared to an age- and health-matched DOC control group. Although quantitative measurement of MRI data on FSG was performed, further analysis was not performed secondary to underenrollment. Cross-calibration of the two MRI scanners was performed with dual imaging of 13 U2P volunteers. Both scanners are operated under quality control and assurance guidelines in accordance with recommendations by the American College of Radiology. A single technician performed all imaging at the RII and a different single technician performed all imaging at WHASC; both technicians were trained by the same neurophysicist to ensure consistency of MRI technique. Neurocognitive test scores on U2P were compared to previously obtained neurocognitive tests on age-matched AFP controls. For test administration consistency, all technicians administering the computerized neurocognitive tests were trained by USAFSAM/FECN. All participants were on active duty status, healthy at the time of examination, and met Flying Class II neurological standards without any medical condition that has been associated with neurological injury. All subjects had received a medical examination within 1 year prior to the study.

The evaluation sequence on each cohort was as follows:

(1) U2P
   a. Demographic, medical, and flight questionnaires
   b. Electronic medical records (EMR) review
   c. Neurocognitive testing
   d. MRI

(2) PHY
   a. Demographic, medical, and chamber questionnaires

b. EMR review
c. MRI

(3) DOC
a. Demographic and medical questionnaires
b. EMR review
c. MRI

(4) FSG
a. Demographic, medical, and flight questionnaires
b. EMR review
c. MRI

(5) AFP – Neurocognitive test scores abstracted from USAFSAM dataset

(6) CAL – Dual imaged on RII and WHASC MRI scanners

All MRI data with PII were entered into the 59MDW clinical image dataset, thus available for future clinical or research use, and a clinical interpretation was placed into the EMR by a neuroradiologist. De-identified MRI data were entered into an AFRL/IRB supervised data repository and were the data used for research analysis. U2P computerized neurocognitive tests with personally identifiable information were added to the clinical neurocognitive dataset maintained by USAFSAM and will be available for future clinical or research use. De-identified computerized neurocognitive tests were entered into an AFRL/IRB supervised data repository and were the data used for research analysis. De-identified demographic, medical, flight history, and chamber history data were entered into an AFRL/IRB supervised data repository.

De-identified MRI fluid-attenuated inversion recovery (FLAIR) and T1 data were co-registered to a common Talairach-atlas-based stereotactic frame (http://www.talairach.org), thus permitting normalization of brain size and hence cross-individual comparison (Figure 1). Briefly, FLAIR images were preprocessed by removal of nonbrain tissue using FSL BET (brain extraction tool), freely available from the Oxford Centre for Functional MRI of the Brain (FMRIB) (Figure 1A). Next, FLAIR images for individual subjects were registered to their corresponding T1-weighted images using FSL FLIRT (FMRIB's linear image registration tool) (Figure 1B) and then registered to a common Talairach-atlas-based stereotactic frame using FSL FLIRT and nine-parameter (three each for rotation, translation, and scaling) global normalization transformation. The purpose of this step is to reduce interindividual anatomical variance in global brain size, shape, and orientation and to permit the use of automated labeling approaches by using a digital brain atlas (Figure 1C). Next, all images were corrected for radio frequency (RF) inhomogeneity artifact using the FSL BET method with default parameters. RF inhomogeneity artifact manifests itself as a low-frequency variation of MRI image intensity that impedes intensity-based image analysis unless corrected. White matter hyperintensities were then manually delineated in three-dimensional (3D)-space using in-house software (http://ric.uthscsa.edu/mango) by a single experienced neuroanatomist blinded for scanner and group information, with high intra-rater (r=0.95) test-retest reproducibility and high inter-rater correlation (r=0.92). During the labeling, WMH regions were coded as ependymal regions contiguous with cerebrospinal fluid (CSF) structures and as subcortical regions as previously described. Finally, the volume and location of WMH were analyzed using the boundaries for the frontal, insula, limbic, occipital, parietal, sublobar, and temporal regions extracted from the digital Talairach atlas (Figure 1D). The volume and number of WMH for U2P were adjusted

using the linear regression coefficients obtained from the calibration study to accommodate for the higher signal-to-noise ratio of the WHASC imaging center.

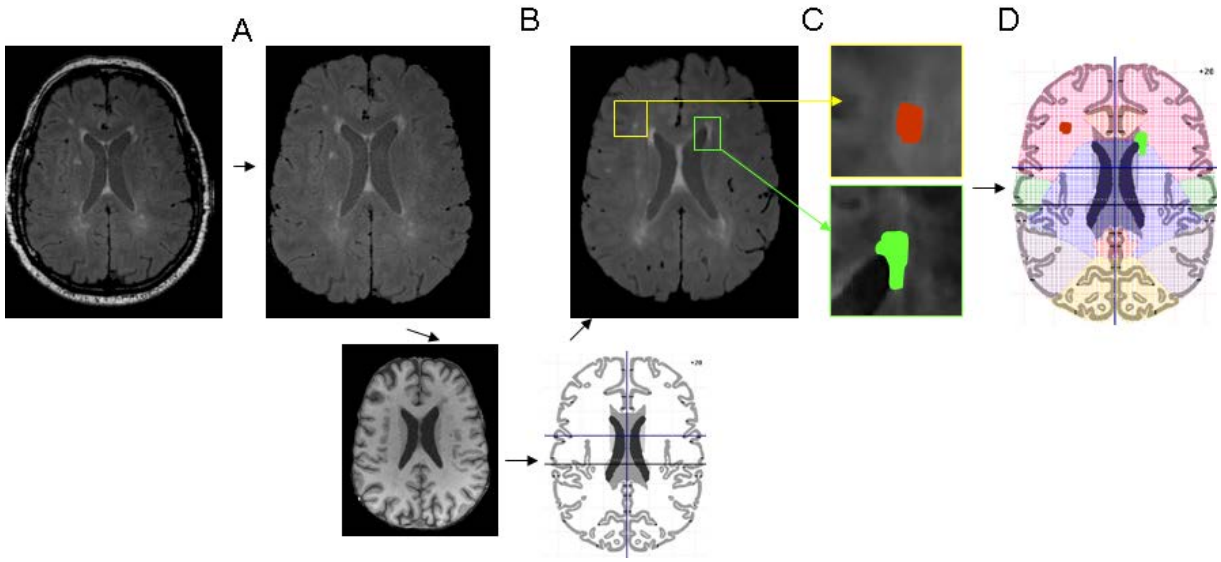


Figure 1. Transformation of MRI for Quantitative Analyses

Computerized neurocognitive data were compared between U2P and AFP. Additionally, comparison of neurocognitive scores within the U2P cohort was performed after separating the cohort into a high and low WMH burden, utilizing as the segregation point the median WMH volume and count identified from the DOC imaging. Finally, comparison of neurocognitive scores within the U2P cohort was performed after segregating the cohort into low-med-high one-third quartiles based on WMH count and volume within the U2P cohort.

3.4 Test Procedures

Both MRI machines utilized the same sequence. No medications or injections were administered. Sequences obtained included T1, FLAIR, arterial spin labeling, diffusion tensor imaging, and magnetic resonance spectroscopy. For this report, sequences analyzed were T1 MPRAGE TR 2200 ms, TE 2.85 ms, isotropic resolution 0.80 mm and FLAIR TR 4500 ms, TE 311 ms, isotropic resolution 1.00 mm. This 3D FLAIR protocol was specifically designed to overcome the limitations of a two-dimensional, thick-slice (5- to 10-mm) clinical imaging protocol and to permit increased detection of smaller lesions with accurate tracing of lesion boundaries. This 3D FLAIR sequence uses a nonselective inversion RF pulse to suppress CSF pulsation artifacts to reduce false-negative hyperintense artifacts seen near CSF-containing structures in the two-dimensional FLAIR sequences.

Computerized neurocognitive tests administered were the Multidimensional Aptitude Battery-II (MAB-II) and the MicroCog: Assessment of Cognitive Functioning (MicroCog). The computer-based MAB-II and MicroCog are neurocognitive assessment tests routinely used in aircrew by the USAF. The MAB-II is a broad-based evaluation of neurocognitive ability based on the Wechsler Adult Intelligence Scale-Revised (WAIS-R; correlation 0.91) [12,13]. This

computer-administered test yields three summary scores (full scale intelligence quotient (IQ), verbal IQ, and performance IQ) based on subtests of vocabulary, arithmetic, information, comprehension, similarities, digit symbol, picture arrangement, object assembly, picture completion, and spatial thinking. Similar to the WAIS-R, the MAB-II full scale, verbal, and performance IQ scores are standardized to age with a mean of 100 and a standard deviation (SD) of 15. Measures of reliability and construct validity for full scale IQ have been shown to be adequate. Results on the MAB-II may inflate IQ estimates, but this systematic bias would be present in all subjects and therefore not affect the group comparisons.

The MicroCog is a computer-based neurocognitive assessment test that consists of 18 subtests used to derive 9 index scores. Level 1 indexes include the five domains of reaction time, memory, attention and control, reasoning and calculation, and spatial processing [14]. Level 2 indexes assess overall information processing speed and information processing accuracy, while Level 3 indexes represent global neurocognitive functioning with general cognitive functioning weighing speed and accuracy equally and general cognitive proficiency weighing accuracy over speed [15-17]. MicroCog was specifically designed to provide more accurate assessment of the reaction time and processing speed when compared to other neurocognitive assessment instruments. However, MicroCog is a computer-based instrument, and more comprehensive neuropsychological testing would be required prior to drawing definitive conclusions about the general cognitive profile of subjects. Nonetheless, normative scores on the MicroCog have been established for age and education level, and overall, MicroCog derived scores show good consistency with other neuropsychological instrument batteries. Finally, since the same test is utilized in both U2P and AFP, any systematic bias would be present in all subjects and therefore not affect group comparisons.

3.5 Statistical Analyses

Statistical analyses were performed with the support of statisticians from USAFSAM and 59MDW. Group-wise analyses of the difference in the volume and number of WMH were performed using a nonparametric Mann-Whitney U-test (Wilcoxon rank sum) two-tailed statistical model. A nonparametric test was used because WMH data are not normally distributed. The Kolmogorov-Smirnov test was used for the equality of continuous one-dimensional probability distribution for comparison of WMH volumes between the PHY and U2P, testing similarity of volumes. The Johnckherre-Terpstra test for ordered alternative hypothesis was used to evaluate DOC $\leq$ PHY $\leq$ U2P WMH volume and count.

The two-tailed Student's t-test with Sidak adjustment for multiple tests was used for comparison of MAB-II and MicroCog between U2P and AFP. Similarly, the two-tailed Student's t-test with Sidak adjustment for multiple tests was used for comparison of MAB-II and MicroCog within U2P separated into low and high WMH volume/count groups. Finally, each U2P one-third quadrant (based on WMH volume/count) neurocognitive test results were compared individually to AFP with Sidak adjustment. Sidak adjustment attempts to correct for the likelihood of a single test being falsely abnormal (type 2 error) when multiple testing is performed.

Analyses of age and hours of exposure to hypobaria versus WMH volume/count were performed utilizing the nonparametric Mann-Whitney U-test (Wilcoxon rank sum) two-tailed statistical model, since WMH values are not parametric. Analyses of age and hours of exposure to hypobaria versus neurocognitive tests were performed using the two-tailed Student's t-test,

since all data are parametric. Analysis of clinical NDCS versus WMH volume/count was performed utilizing the Mann-Whitney U-test.

The threshold for significance was set as $p < 0.05$, with all statistical tests evaluated as two-tailed.

4.0 RESULTS

4.1 MRI Results

Since insufficient FSG were enrolled to permit valid study conclusions, no further analysis of FSG was performed.

An increased amount of subcortical WMH burden was apparent in U2P both with and without clinical symptoms of NDCS (Figure 2). A similar increased amount of WMH burden was apparent in PHY, again with and without clinical NDCS symptoms (Figure 3).

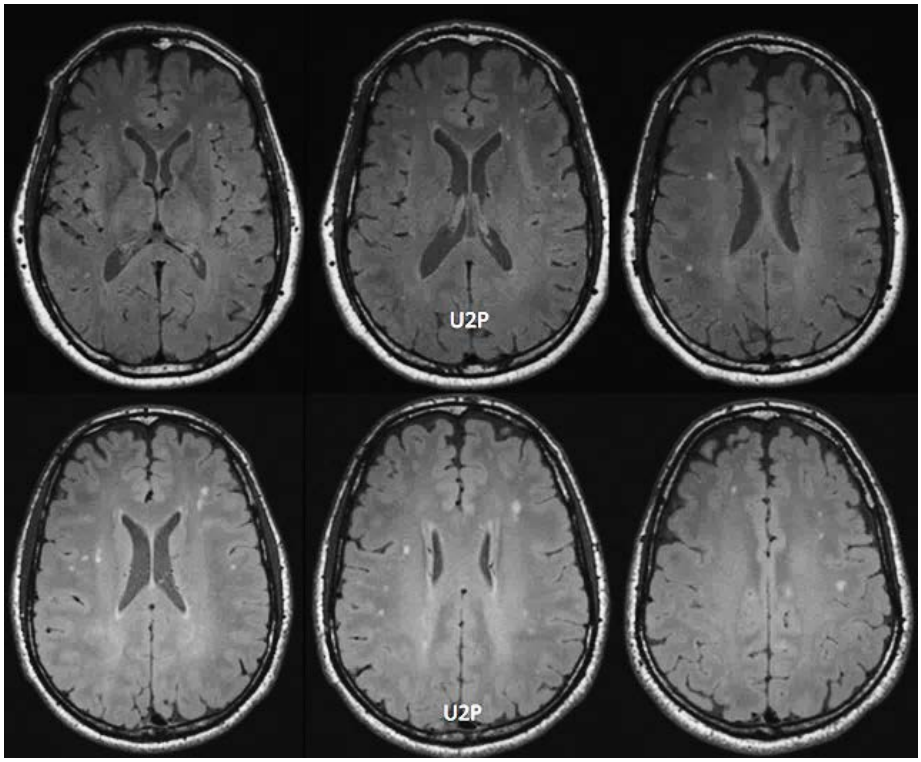


Figure 2. WMH in U2P with (Upper Row) and without (Lower Row) Clinical NDCS Symptoms

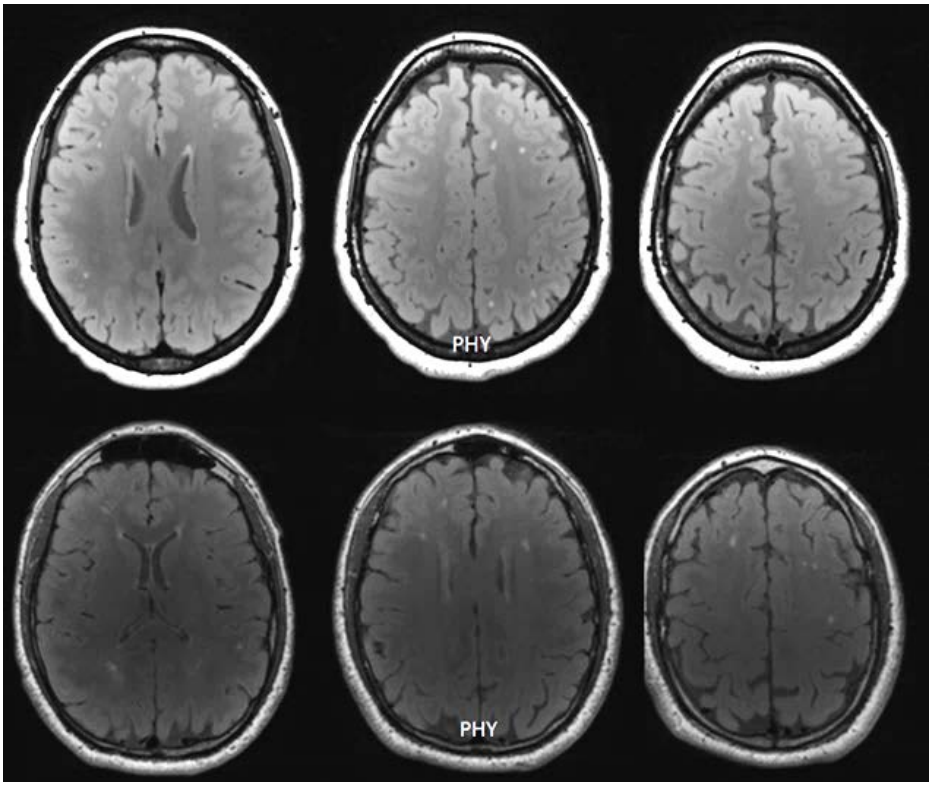


Figure 3. WMH in PHY with (Upper Row) and without (Lower Row) NDCS Symptoms

Quantitative analysis of WMH burden in U2P and PHY compared to DOC demonstrated significant differences in both WMH volume and count between U2P:DOC and PHY:DOC but not between U2P:PHY (Table 1). Furthermore, within the U2P cohort, those with clinical NDCS had a higher subcortical WMH burden than those without, although the statistical significance was not as robust (Table 2).

Table 1. Quantitative WMH Burden in DOC, PHY, and U2P

WMH	DOC (n=162) (mean±SD)	PHY (n=83) (mean±SD)	U2P (n=105) (mean±SD)	Mann-Whitney-Wilcoxon Significance (2-tailed)		
				DOC:PHY	DOC:U2P	U2P:PHY
Volume (mL)	0.034±0.057	0.126±0.404	0.147±0.296	p=0.020	p<0.001	p=0.237
Count	2.7±3.1	6.4±11.1	9.7±18.3	p=0.040	p<0.001	p=0.091

The qualitative distribution of the cohort superimposed WMH burden in DOC, PHY, and U2P suggested a diffuse pattern of increase with an apparent qualitative difference of DOC < PHY < U2P (Figure 4). Quantitative analyses demonstrated similar results for WMH volume, although the Kolmogorov-Smirnov test demonstrated no statistical difference between PHY and U2P (p=0.388). The Johnckherre-Terpstra test demonstrated an ordering of DOC < PHY ≤ U2P on WMH volume (p=0.024) and count (p=0.012), while again for PHY < U2P the difference was not significant.

Table 2. Quantitative WMH Burden in U2P Separated into with and without Clinical NDCS

WMH	All U2P (n=50) (mean±SD)	NDCS U2P (n=12) (mean±SD)	No NDCS U2P (n=38) (mean±SD)	Mann-Whitney-Wilcoxon Significance (1-tailed) DOC:PHY
Total volume (mL)	1.05±0.54	1.37±0.79	0.95±0.37	p=0.026
Subcortical volume (mL)	0.07±0.12	0.13±0.14	0.05±0.11	p=0.059
Insula lobe volume (mL)	0.006±0.021	0.020±0.038	0.001±0.005	p=0.018
Count	3.76±6.10	7.25±10.66	2.66±2.85	p=0.149

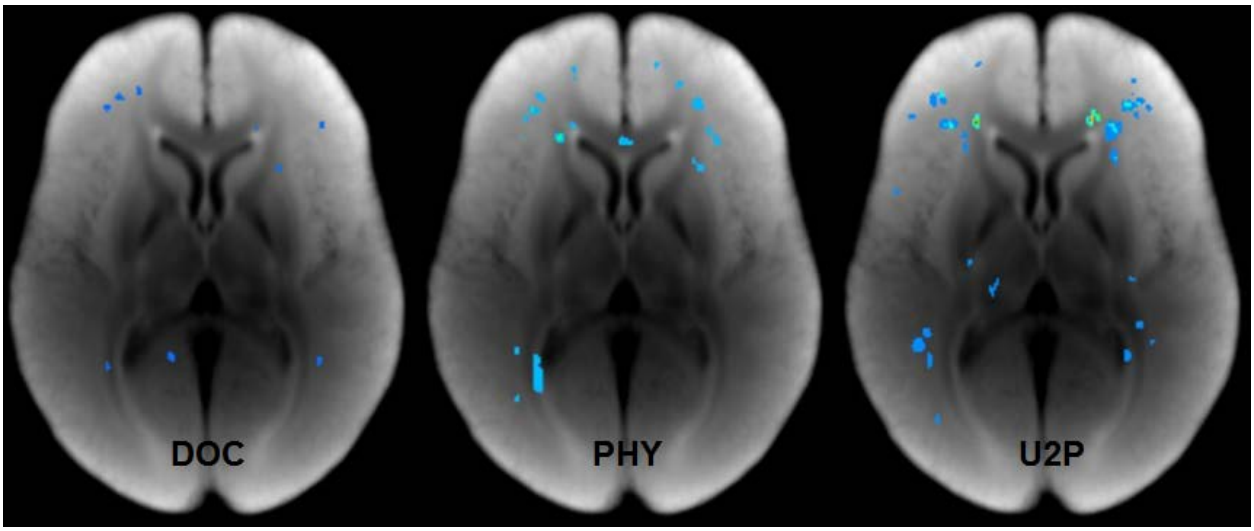
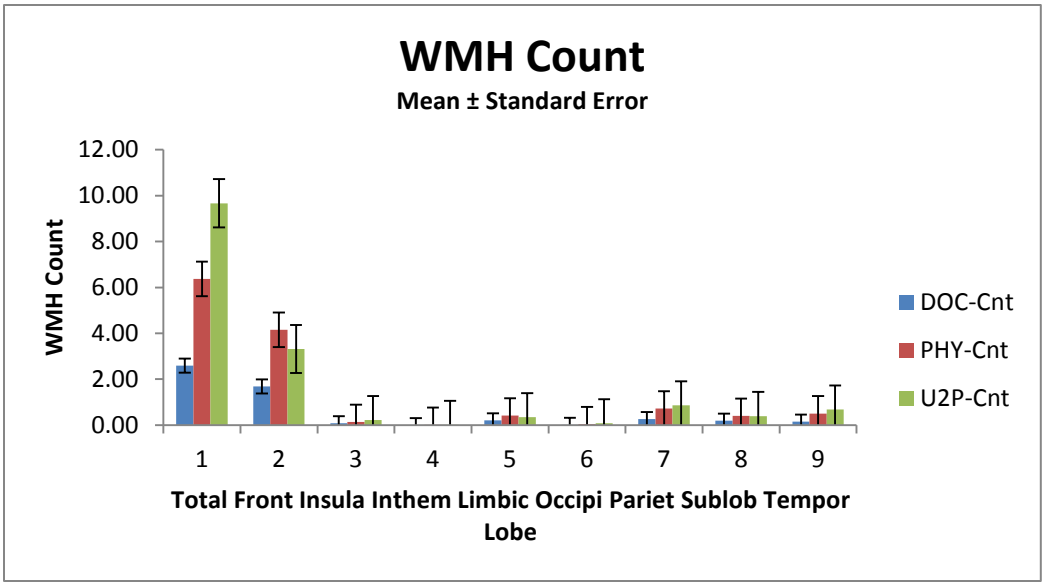


Figure 4. Qualitative Cohort-Wide Distribution of WMH Burden

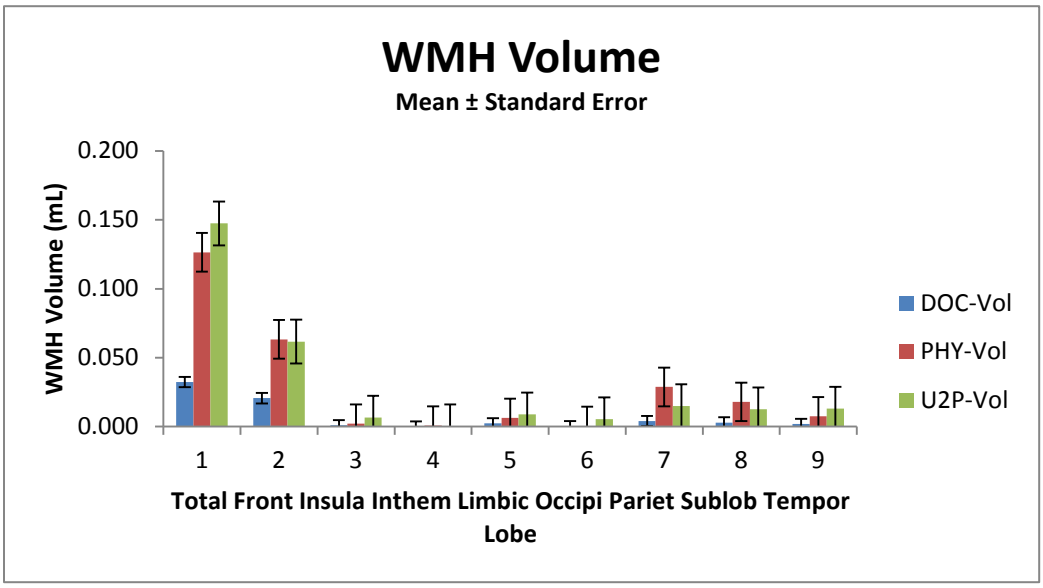
Quantitative analyses of WMH burden (volume and count) demonstrated a generalized increase in all lobes with a significant difference in total and in frontal lobe WMH burden between DOC versus PHY and U2P but not between PHY and U2P (Figures 5 and 6). Absolute values revealed WMH volume/count DOC < PHY < U2P in seven of nine quartiles, suggesting a larger sample size would demonstrate a statistical difference between PHY and U2P.

The Spearman correlation between PHY and U2P WMH burden and age or total hours of exposure to hypobaria was low, suggesting age and total hours of exposure were responsible for relatively little of the WMH burden in these cohorts (Table 3).



Total=total subcortical WMH; Front=frontal; Insula=insula; Inthem=interhemispheric; Limbic=limbic; Occipi=occipital; Pariet=parietal; Sublob=sublobar; Tempor=temporal

Figure 5. Distribution by Lobe of Increased WMH Burden Volume



Total=total subcortical WMH; Front=frontal; Insula=insula; Inthem=interhemispheric; Limbic=limbic; Occipi=occipital; Pariet=parietal; Sublob=sublobar; Tempor=temporal

Figure 6. Distribution by Lobe of Increased WMH Burden Count

Table 3. Correlation of WMH Burden to Age and Total Hours of Hypobaric Exposure

Group	Mean/Median	Spearman's Correlation Coefficient rho for--	
		WMH Volume	WMH Count
Age			
DOC (n=148)	34.6/33.0	0.189	0.205
PHY (n=83)	36.5/36	0.084	0.018
U2P (n=105)	37.7/37.5	0.142	0.124
Hours Exposure			
PHY (n=83)	96.9/72.5	-0.002	-0.065
U2P (n=105)	741/667	0.144	0.122

4.2 Neurocognitive Test Results

At time of entry into undergraduate pilot training (UPT), baseline MAB-II demonstrated no significant difference between U2P and AFP (Table 4). Likewise, no significant difference was present in the Air Force Officer Qualifying Test (AFOQT) score between U2P and AFP ($p>0.05$). No difference in current MAB-II test scores was detected between U2P and AFP (Table 5). However, significant difference was present on current Microcog, with U2P having lower scores on reasoning/calculation, memory, information processing accuracy, and general cognitive functioning and a trend towards lower performance on general cognitive proficiency after applying Sidak adjustment for multiple tests (Table 6).

Table 4. MAB-II Comparison Between U-2 Pilots and USAF Pilot Controls at Entry into UPT

MAB-II Baseline	U2P (n=62) (mean±SD)	AFP (n=83) (mean±SD)	t-test (2-tailed) Significance	Sidak (2-tailed) Significance
Verbal IQ[a]	118.9±7.0	119.6±6.4	p=0.498	p=0.874
Performance IQ[a]	117.2±14.9	120.7±8.0	p=0.067	p=0.189
Full Scale IQ[a]	120.1±7.3	121.5±6.0	p=0.212	p=0.511
Information[b]	68.1±6.3	67.4±5.6	p=0.546	p=1.000
Comprehension[b]	59.5±5.2	59.9±3.6	p=0.593	p=1.000
Arithmetic[b]	60.2±7.0	61.5±6.9	p=0.279	p=0.962
Similarities[b]	59.6±5.1	60.6±3.9	p=0.195	p=0.886
Vocabulary[b]	59.5±6.8	60.0±7.0	p=0.680	p=1.000
Digit Symbol[b]	64.5±8.0	66.8±7.5	p=0.090	p=0.611
Picture Completion[b]	60.7±6.0	61.0±6.0	p=0.819	p=1.000
Spatial[b]	60.1±6.7	61.5±6.6	p=0.216	p=0.912
Picture Arrangement[b]	50.9±7.5	54.5±6.9	p=0.005	p=0.049
Object Assembly[b]	60.7±4.8	62.6±5.6	p=0.042	p=0.349

[a]Standard score.
[b]T-score.

Table 5. MAB-II Comparison Between U-2 Pilots and USAF Pilot Controls

MAB-II	U2P[a] (n=87) (mean±SD)	AFP[a] (n=83) (mean±SD)	t-test (2-tailed) Significance	Sidak (2-tailed) Significance
Verbal IQ[b]	120.7±5.9	121.3±6.0	p=0.516	p=0.887
Performance IQ[b]	127.5±9.0	128.0±6.7	p=0.680	p=0.967
Full Scale IQ[b]	125.5±6.8	126.3±5.5	p=0.442	p=0.826
Information[c]	67.5±6.7	68.2±6.0	p=0.459	p=0.998
Comprehension[c]	59.7±3.5	60.3±3.2	p=0.245	p=0.940
Arithmetic[c]	61.3±6.2	62.9±6.6	p=0.095	p=0.632
Similarities[c]	61.6±4.5	62.5±3.7	p=0.129	p=0.748
Vocabulary[c]	61.1±5.1	61.4±6.0	p=0.771	p=1.000
Digit Symbol[c]	66.0±9.0	69.3±5.9	p=0.007	p=0.073
Picture Completion[c]	65.1±5.7	65.8±5.8	p=0.421	p=0.996
Spatial[c]	63.2±7.2	62.6±6.3	p=0.592	p=1.000
Picture Arrangement[c]	58.4±9.1	57.4±7.5	p=0.435	p=0.997
Object Assembly[c]	65.9±6.0	66.5±4.9	p=0.489	p=0.999

[a]Age 28-47.
[b]Standard score.
[c]T-score.

Table 6. MicroCog Comparison Between U-2 Pilots and USAF Pilot Controls

Level	MicroCog	U2P[a] (n=93) (mean±SD)	AFP[a] (n=80) (mean±SD)	t-test (2-tailed) Significance	Sidak (2-tailed) Significance
1	Attention/mental control	104.4±9.3	103.8±10.8	p=0.696	p=0.997
1	Reasoning/calculation	99.4±12.5	106.5±10.9	p<0.001	p=0.001
1	Memory	105.5±12.5	110.9±13.7	p=0.007	p=0.036
1	Spatial processing	109.1±9.4	109.1±9.4	p=0.989	p=1.000
1	Reaction time	107.3±6.7	104.8±9.2	p=0.047	p=0.216
2	Information processing speed	103.6±12.5	106.5±10.5	p=0.100	p=0.189
2	Information processing accuracy	102.1±9.8	105.8±10.0	p=0.016	p=0.032
3	General cognitive functioning	103.5±10.0	108.5±10.6	p=0.002	p=0.004
3	General cognitive proficiency	105.4±9.4	108.6±10.2	p=0.037	p=0.072

Note: All scores standard scores.
[a]Age 28-47.

The U2P cohort was segregated into a high versus low WMH burden utilizing the median DOC WMH after making the assumption that young to middle age healthy adults would have a similar WMH burden across age- and health-matched groups in the absence of a causative factor such as hypobaric exposure. No significant difference was detected on MAB-II (Table 7). However, a significant difference was detected on Microcog, with the higher WMH burden cohort having lower performance on reason/calculation, memory, general cognitive functioning and general cognitive proficiency (WMH count) and with a trend noted in information processing accuracy (WMH count/volume) after Sidak adjustment for multiple tests (Table 8).

Table 7. MAB-II Comparison Between U-2 Pilots with High versus Low WMH Burden

MAB-II	Lower WMH		Upper WMH		t-test (2-tailed) Significance		Sidak (2-tailed) Significance	
	Count (n=31) (mean±SD)	Volume (n=29) (mean±SD)	Count (n=62) (mean±SD)	Volume (n=64) (mean±SD)	Count	Volume	Count	Volume
Verbal IQ[a]	122.0±4.9	122.0±5.1	120.1±6.2	120.1±6.0	p=0.146	p=0.147	p=0.377	p=0.379
Performance IQ[a]	127.6±8.9	128.7±8.7	127.5±9.0	127.0±9.0	p=0.978	p=0.400	p=1.000	p=0.784
Full Scale IQ[a]	126.4±6.6	127.0±6.6	125.1±6.9	124.9±6.8	p=0.434	p=0.177	p=0.819	p=0.443
Information[b]	69.2±4.9	69.2±4.7	66.6±7.2	66.7±7.2	p=0.092	p=0.123	p=0.619	p=0.731
Comprehension[b]	60.3±2.9	60.0±3.1	59.4±3.7	59.6±3.6	p=0.318	p=0.654	p=0.978	p=1.000
Arithmetic[b]	61.5±5.1	61.4±5.8	61.2±6.7	61.2±6.4	p=0.791	p=0.916	p=1.000	p=1.000
Similarities[b]	61.7±4.2	62.2±4.3	61.5±4.6	61.3±4.5	p=0.818	p=0.389	p=1.000	p=0.993
Vocabulary[b]	62.8±4.8	62.8±4.6	60.4±5.0	60.4±5.1	p=0.042	p=0.041	p=0.349	p=0.342
Digit Symbol[b]	68.3±6.3	68.1±6.5	65.0±9.8	65.1±9.6	p=0.111	p=0.165	p=0.692	p=0.835
Picture Completion[b]	64.8±5.0	65.4±4.3	65.2±6.0	65.0±6.2	p=0.733	p=0.727	p=1.000	p=1.000
Spatial[b]	62.5±7.6	63.2±7.8	63.5±6.9	63.1±6.8	p=0.556	p=0.953	p=1.000	p=1.000
Picture Arrangement[b]	57.6±9.3	59.2±8.5	58.8±9.0	58.1±9.3	p=0.551	p=0.630	p=1.000	p=1.000
Object Assembly[b]	66.0±5.4	66.6±5.4	65.8±9.0	65.6±6.1	p=0.863	p=0.476	p=1.000	p=0.998

[a]Standard score.
[b]T-score.

Table 8. MicroCog Comparison Between U-2 Pilots with High versus Low WMH Burden

Level	MicroCog	Lower WMH		Upper WMH		t-test (2-tailed) Significance		Sidak (2-tailed) Significance	
		Count (n=33) (mean±SD)	Volume (n=30) (mean±SD)	Count (n=60) (mean±SD)	Volume (n=63) (mean±SD)	Count	Volume	Count	Volume
1	Attention/mental control	104.8±6.7	104.7±7.2	104.2±10.4	104.2±10.1	p=0.808	p=0.806	p=1.000	p=1.000
1	Reasoning/ calculation	104.1±11.3	101.8±11.7	96.8±12.3	98.2±12.6	p=0.009	p=0.197	p=0.044	p=0.666
1	Memory	110.2±11.0	108.8±12.5	102.9±12.4	103.9±12.1	p=0.006	p=0.075	p=0.030	p=0.323
1	Spatial processing	111.0±8.3	110.9±8.3	108.1±9.8	108.3±9.7	p=0.161	p=0.202	p=0.584	p=0.676
1	Reaction time	108.4±6.1	109.5±5.4	106.7±6.9	106.2±7.0	p=0.299	p=0.028	p=0.831	p=0.132
2	Information processing speed	106.7±11.5	1047±13.3	101.9±12.5	103.0±11.9	p=0.101	p=0.534	p=0.192	p=0.783
2	Information processing accuracy	105.0±7.9	105.2±8.6	100.5±10.2	100.7±9.9	p=0.029	p=0.036	p=0.057	p=0.071
3	General cognitive functioning	107.2±8.9	106.1±9.8	101.5±9.8	102.3±9.7	p=0.010	p=0.081	p=0.020	p=0.155
3	General cognitive proficiency	108.8±8.6	107.6±9.0	103.6±9.3	104.4±9.4	p=0.011	p=0.121	p=0.022	p=0.227

Note: All scores standard scores.

Furthermore, after separating the U2P cohort into three quartiles, no difference in neurocognitive test performance was present between the low quartile and AFP controls after Sidak adjustment (Tables 9 and 10). However, there were significant differences between the mid quartile and AFP controls for WMH burden count (reasoning/calculation, memory, information processing accuracy, general cognitive functioning, and general cognitive proficiency) and WMH burden volume (reasoning/calculation, information processing accuracy, and general cognitive functioning) and between the AFP controls and the upper quartile for WMH burden count (reasoning/calculation, information processing accuracy, and global cognitive functioning) and WMH burden volume (reasoning/calculation, information processing

speed, and global cognitive functioning). Additionally, a trend was noted in the WMH burden count for global cognitive proficiency (upper quadrant) and in the WMH burden volume for memory (mid quadrant memory and upper quadrant).

Table 9. MicroCog Comparison Between U-2 Pilot WMH Count Quartiles (Low – Mid – High) and USAF Pilot Controls

Level	MicroCog (current)	AFP (n=80) (mean±SD)	U2P Low (n=31)			U2P Mid (n=31)			U2P High (n=31)		
			Mean±SD	t-test 2-tailed	Sidak	Mean±SD	t-test 2-tailed	Sidak	Mean±SD	t-test 2-tailed	Sidak
	Mean WMH count		0.4			4.1			24.1		
1	Attention/ mental control	103.8±10.8	104.5±6.8	p=0.741	p=0.999	105.1±9.7	p=0.569	p=0.985	103.6±10.8	p=0.940	p=1.000
1	Reasoning/ calculation	106.5±10.9	103.7±11.5	p=0.239	p=0.745	96.7±12.3	p<0.001	p=0.001	97.7±12.3	p<0.001	p=0.002
1	Memory	110.9±13.7	110.5±11.3	p=0.890	p=1.000	101.3±13.5	p=0.001	p=0.005	104.6±10.6	p=0.025	p=0.119
1	Spatial processing	109.1±9.4	111.3±8.4	p=0.278	p=0.804	108.4±8.7	p=0.703	p=0.998	107.7±10.5	p=0.492	p=0.966
1	Reaction time	104.8±9.2	108.5±5.4	p=0.038	p=0.176	106.0±7.7	p=0.521	p=0.975	107.2±6.5	p=0.196	p=0.664
2	Information processing speed	106.5±10.5	106.3±11.4	p=0.931	p=0.995	102.0±11.7	p=0.056	p=0.109	102.4±13.5	p=0.091	p=0.174
2	Information processing accuracy	105.8±10.0	105.2±8.0	p=0.777	p=0.950	100.8±10.4	p=0.021	p=0.042	100.4±9.8	p=0.012	p=0.024
3	General cognitive functioning	108.5±10.6	107.1±9.1	p=0.524	p=0.773	101.9±10.2	p=0.004	p=0.008	101.6±9.4	p=0.002	p=0.004
3	General cognitive proficiency	108.6±10.2	109.0±8.7	p=0.839	p=0.974	103.4±10.0	p=0.017	p=0.034	103.9±8.4	p=0.027	p=0.053

Note: All scores standard scores.

Table 10. MicroCog Comparison Between U-2 Pilot WMH Volume Quartiles (Low – Mid – High) and USAF Pilot Controls

Level	MicroCog (current)	AFP (n=80) (mean±SD)	U2P Low (n=31)			U2P Mid (n=31)			U2P High (n=31)		
			Mean±SD	t-test 2-tailed	Sidak	Mean±SD	t-test 2-tailed	Sidak	Mean±SD	t-test 2-tailed	Sidak
	Mean WMH Volume (cm^3)		0.003			0.037			0.389		
1	Attention/ mental control	103.8±10.8	104.5±7.1	p=0.719	p=0.998	103.5±8.1	p=0.912	p=1.000	105.1±11.8	p=0.590	p=0.988
1	Reasoning/ calculation	106.5±10.9	101.1±12.2	p=0.026	p=0.123	97.5±13.0	p<0.001	p=0.002	99.5±11.9	p=0.004	p=0.020
1	Memory	110.9±13.7	108.7±12.4	p=0.435	p=0.942	104.2±12.0	p=0.018	p=0.087	103.6±12.4	p=0.012	p=0.059
1	Spatial processing	109.1±9.4	110.6±8.4	p=0.460	p=0.954	109.5±8.5	p=0.872	p=1.000	107.3±10.8	p=0.387	p=0.913
1	Reaction time	104.8±9.2	109.1±5.7	p=0.019	p=0.092	104.0±7.4	p=0647	p=0.995	108.7±5.6	p=0.030	p=0.141
2	Information processing speed	106.5±10.5	104.7±13.1	p=0.468	p=0.717	105.1±9.2	p=0.521	p=0.771	100.8±13.9	p=0.024	p=0.047
2	Information processing accuracy	105.8±10.0	104.3±9.8	p=0.478	p=0.728	99.3±10.0	p=0.003	p=0.006	102.8±8.6	p=0.151	p=0.279
3	General cognitive functioning	108.5±10.6	105.6±10.1	p=0.199	p=0.358	102.7±9.6	p=0.010	p=0.020	102.3±9.8	p=0.006	p=0.012
3	General cognitive proficiency	108.6±10.2	107.1±9.3	p=0.496	p=0.746	104.7±8.8	p=0.067	p=0.130	104.5±9.8	p=0.057	p=0.111

Note: All scores standard scores.

5.0 DISCUSSION

This study demonstrated an increased subcortical WMH burden in age- and health-matched PHY and U2P compared to DOC with DOC < PHY ≤ U2P. The only identified cohort difference was the occupational hypobaric experience present in PHY and U2P; while U2P also

have exposure to other environmental factors such as radiation, PHY lack this exposure. Although statistically no difference was demonstrated between PHY and U2P, higher absolute values in seven of nine quadrants in U2P compared to PHY suggest the possibility of a "dose curve" with the higher exposure of the U2P causing greater injury than the lower exposure of PHY. However, no simple relationship between total hours of exposure and degree of WMH burden was demonstrated. The hypobaric experience is complex and includes the pre-exposure nitrogen degassing while on 100% O_2, duration and activity at altitude, and the frequency of exposure. The anatomical distribution of the increased WMH burden is diffuse, roughly corresponding to the volume of lobar tissue, suggesting the possibility of a microembolic shower. Based on published literature noting a relatively infrequent occurrence of macroemboli > 30μm and the pattern of distribution to small arterioles seen in this study, we postulate these microemboli are < 30 μm in size. While we believe the initial event is related to venous nitrogen gas bubbles, unknown is how these convert to arterial microemboli and whether these arterial microemboli are nitrogen gas bubbles, platelet-thrombin aggregates, or "macro" microparticles with activation of inducible nitric oxide synthase. While we postulate initial injury is to axonal myelin, the pathophysiological mechanism underlying this injury remains unclear. Also unknown is whether this initial injury is intra- or extracellular and whether it is ischemic injury or inflammatory injury. Finally, still unknown is whether this injury leads to an up regulation of inflammatory genes and, if so, the time course and impact of this up regulation. We postulate the FLAIR changes (manifested as increased WMH burden) reflect the "intensity" of exposure, which appears to be multifactor including innate reparative processes representing biodiversity of subjects, duration of exposure and physical activity while at altitude, and frequency of exposure and recovery time. While this injury appears related to the hypobaric exposure experience, it is also unclear what induces the injury, whether it is hypobaria, the pre-exposure hyperoxemia from the necessary nitrogen degassing, or some other factor associated with the hypobaric exposure experience.

The neurocognitive test scores demonstrate that the U2P group has an acquired lower test performance than the AFP group, presumably related to the repeated exposure to the hypobaric experience in U2P. However, not every U2P subject demonstrates this difference. Both cohorts at time of entry into UPT had similar MAB-II and AFOQT scores, suggesting no inherent difference in U2P vs. AFP initially. U2P have been assigned to multiple platforms including fighter/high performance 75% (79/106), and heavy 92% (97/106), again suggesting no initial cohort difference at time of exit from UPT. While within U2P the correlation between neurocognitive test scores and WMH burden trends towards lower scores with higher WMH burden, a direct association between WMH and neurocognitive test scores cannot be made since the AFP did not also undergo MRI study. The pattern of lower neurocognitive scores in U2P are similar to that seen in other white matter diseases and injury and include lower performance on reasoning/calculation, memory, information processing accuracy, and general cognitive functioning with a trend in general cognitive proficiency. However, since the Microcog is computer-based, reaction time is an important factor. Although standards have been established for USAF pilots, a conclusion of decreased general cognitive functioning and proficiency cannot be made without a clinical assessment.

This study was successful in demonstrating previously unrecognized subcortical brain injury occurring in individuals occupationally exposed to repetitive hypobaric experience even in the absence of clinical symptoms of NDCS. Furthermore, while all U2P remain without clinical deficit, this study did demonstrate an apparent association between WMH burden and

neurocognitive test performance in U2P. The future clinical significance of these findings in high functioning individuals with significant cognitive reserve remains unknown.

This study generated additional data for future analyses that include cortical structural mapping, neurochemical markers, arterial flow, and fiber bundle integrity. Additionally, this study identified a need for a relevant animal model for better understanding of the pathophysiological mechanisms, risk factors, potential mitigating and/or treatment modalities, and chronic impact on functioning. Continuing analysis of these other datasets and the in-progress animal model will be subsequently reported in the literature.

Peer-reviewed publications associated with this study are as follows:

1. McGuire SA, Sherman PM, Brown AC, Robinson AY, Tate DF, Fox PT, et al. Hyperintense white matter lesions in 50 high-altitude pilots with neurologic decompression sickness. Aviat Space Environ Med 2012; 83(12):1117-22.
2. McGuire S, Sherman P, Profenna L, Grogan P, Sladky J, Brown A, et al. White matter hyperintensities on MRI in high-altitude U-2 pilots. Neurology 2013; 81(8):729-35.
3. McGuire S, Tate D, Wood J, et al. Lower neurocognitive function in U-2 pilots: relationship to white matter hyperintensities. (In final review of revisions)
4. McGuire S, Sherman P, Wijtenburg S, et al. White matter hyperintensities and hypobaric exposure. (Submitted for peer review)

6.0 CONCLUSION

Subcortical cerebral injury is occurring in individuals occupationally exposed to the hypobaric experience even in the absence of clinical NDCS. Furthermore, lower performance on neurocognitive tests appears associated with this WMH burden. This study raises concern for any military member occupationally exposed to hypobaric pressures. This study identifies areas for future research in pursuit of a better understanding of this injury.

7.0 REFERENCES

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LIST OF ABBREVIATIONS AND ACRONYMS

3D	three-dimensional
AFOQT	Air Force Officer Qualifying Test
AFP	Air Force pilot control
AFRL	Air Force Research Laboratory
CAL	MRI calibration
CSF	cerebrospinal fluid
DOC	doctorate degree control
EMR	electronic medical record
FECN	Neuropsychiatry Branch, Aeromedical Consult Service, USAFSAM
FLAIR	fluid-attenuated inversion recovery
FMRIB	Oxford Centre for Functional MRI of the Brain
FSG	flight surgeon
FSL BET	brain extraction tool
FSL FLIRT	FMRIB's linear image registration tool
IQ	intelligence quotient
IRB	Institutional Review Board
MAB-II	Multidimensional Aptitude Battery-II
MDW	Medical Wing
MRI	magnetic resonance imaging
NDCS	neurologic decompression sickness
PHY	altitude chamber personnel
RF	radio frequency
RII	Research Imaging Institute
SD	standard deviation
U2P	U-2 pilots
UPT	undergraduate pilot training
USAF	U.S. Air Force
USAFSAM	U.S. Air Force School of Aerospace Medicine
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WHASC	Wilford Hall Ambulatory Surgery Clinic
WMH	white matter hyperintensities